EXHIBIT 10

ABBOTT

FROM: [redacted] NC
D-305, A-1

INTEROFFICE CORRESPONDENCE

DATE: November 29, 1982

PHARMACEUTICAL PRODUCTS DIVISION
PROMOTIONAL LITERATURE APPROVAL NOTICE

ITEM: DEPAKENE - Letter, enclosure & envelope

COMMODITY NUMBER: 212504 P. O. NUMBER: 93A-055902

DATE RECEIVED: QUANTITY: (Ctns.)

VENDOR: Nesco

FORWARD TO: Dept. 444 Quality Assurance Adm. Svcs. PPD (R1 B 8th)

Copy Approved by: R E Wilson Date: 11/30/82

Return to: ~~Wm. Schramm~~ E Lopez
D-305, NC

EXHIBIT
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4-29-14 MS

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
North Chicago, Illinois 60064

Dear Doctor:

RE: PREGNANCY AND VALPROIC ACID (DEPAKENE®)

New data concerning the potential teratogenicity of Depakene have recently been brought to our attention by a Letter to the Editor in The Lancet of October 23, 1982. A review of the same data appeared in a bulletin issued jointly by the Food and Drug Administration and the Centers for Disease Control (CDC) in the Morbidity and Mortality Weekly Report of October 29, 1982.

According to these reports, data collected in the Rhone Valley area of France indicate a higher than normal incidence of spina bifida in the offspring of epileptic mothers who received valproate therapy during the first trimester of pregnancy. Based upon this single preliminary report, the CDC has estimated the risk of valproic acid exposed women having children with spina bifida to be approximately 1.2%. This risk is similar to that for non-epileptic women who have had children with neural tube defects. While no confirmatory data have been found in other birth registries, which may be due to the limited number of valproate exposures evaluable in these populations, we nevertheless feel it appropriate to bring this preliminary report to your attention at this time since there are prenatal counseling centers for women who may have an increased risk of having children with spina bifida.

As you are well aware, the fetus of a pregnant epileptic woman is at an increased risk of serious malformation both as a result of the disease itself and because of various anticonvulsant drugs utilized in treatment. All anticonvulsants carry a warning of potential human teratogenicity in their labeling. Some of these drugs, i.e., phenytoin, trimethadione, paramethadione and valproic acid, have now been associated with increased risk of specific congenital defects.

On the basis of the above mentioned preliminary data, we have made certain revisions in the "Use in Pregnancy" section of our Depakene package insert. A copy of this revised insert is included for your information.

Sincerely,

John G Page, M.D.

John G. Page, M.D., F.A.A.P.
Medical Director, Medical Affairs
(312) 937-3400

JGP-F2

(Nos. 5681 and 5682)
212504
97-0210/R1—223—Dec., 1982

DEPAKENE®

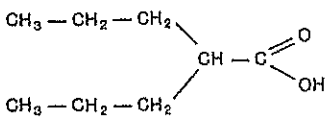
VALPROIC ACID

CAPSULES and SYRUP

WARNING:
HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING DEPAKENE. THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT WITH DEPAKENE. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS LOSS OF SEIZURE CONTROL, MALAISE, WEAKNESS, LETHARGY, ANOREXIA AND VOMITING. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

DESCRIPTION

DEPAKENE (valproic acid) is a carboxylic acid designated as 2-propylpentanoic acid. It is also known as dipropylacetic acid. DEPAKENE has the following structure:



Valproic acid (pKa 4.6) has a molecular weight of 144 and occurs as a colorless liquid with a characteristic odor. It is slightly soluble in water (1.8 mg/ml) and very soluble in organic solvents.

DEPAKENE is supplied as soft elastic capsules and syrup for oral administration. Each capsule contains 250 mg valproic acid. The syrup contains the equivalent of 250 mg valproic acid per 5 ml as the sodium salt.

CLINICAL PHARMACOLOGY

DEPAKENE is an antiepileptic agent which is chemically unrelated to other drugs used to treat seizure disorders. It has no nitrogen or aromatic moiety characteristic of other antiepileptic drugs. The mechanism by which DEPAKENE exerts its antiepileptic effects has not been established. It has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA). The effect on the neuronal membrane is unknown.

DEPAKENE is rapidly absorbed after oral administration. Peak serum levels of valproic acid occur approximately one to four hours after a single oral dose of DEPAKENE. The serum half-life of the parent compound is typically in the range of six to sixteen hours. Half-lives in the lower part of the above range are usually found in patients taking other antiepileptic drugs. A slight delay in absorption occurs when the drug is administered with meals but this does not affect the total absorption.

Valproic acid is rapidly distributed and at therapeutic drug concentrations, drug is highly bound (90%) to human plasma proteins. Increases in dose may result in decreases in the extent of protein binding and variable changes in valproate clearance and elimination.

Elimination of DEPAKENE and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine. The drug is primarily metabolized in the liver and is excreted as the glucuronide conjugate. Other metabolites in the urine are products of beta, omega-1, and omega oxidation (C-3, C-4, and C-5 positions). The major oxidative metabolite in the urine is 2-propyl-3-keto-pentanoic acid; minor metabolites are 2-propyl-glutaric acid, 2-propyl-5-hydroxypentanoic acid, 2-propyl-3-hydroxypentanoic acid and 2-propyl-4-hydroxypentanoic acid.

INDICATIONS

DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple (petit mal) and complex absence seizures. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE "WARNINGS" SECTION FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

CONTRAINDICATIONS

DEPAKENE (VALPROIC ACID) SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT DYSFUNCTION.

DEPAKENE is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE. These incidents usually have occurred during the first six months of treatment with DEPAKENE. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia and vomiting. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering DEPAKENE to patients with a prior history of hepatic disease. Patients with various unusual congenital disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug. The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Usage in Pregnancy: ACCORDING TO RECENT REPORTS IN THE MEDICAL LITERATURE, DEPAKENE MAY PRODUCE TERATOGENICITY IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY. THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. BASED UPON A SINGLE FRENCH REPORT[1] THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1.2%.[2] THIS RISK IS SIMILAR TO THAT FOR NONEPILEPTIC WOMEN WHO HAVE HAD CHILDREN WITH NEURAL TUBE DEFECTS (ANENCEPHALY AND SPINA BIFIDA).

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPTIC DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

ANIMAL STUDIES HAVE ALSO DEMONSTRATED DEPAKENE INDUCED TERATOGENICITY. Studies in rats and human females demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

Antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS

Hepatic Dysfunction: See "Contraindications" and "Warnings" sections.

General: Because of reports of thrombocytopenia and inhibition of the secondary phase of platelet aggregation, platelet counts and bleeding time determination are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKENE be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKENE dosage or withdrawal of therapy pending investigation.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. If elevation occurs, DEPAKENE should be discontinued.

Since DEPAKENE (valproic acid) may interact with concurrently administered antiepileptic drugs, periodic serum level determinations of concomitant antiepileptic drugs are recommended during the early course of therapy. (See "Drug Interactions" section).

DEPAKENE is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

Information for Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: DEPAKENE may potentiate the CNS depressant activity of alcohol.

THERE IS EVIDENCE THAT DEPAKENE CAN CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS BY IMPAIRMENT OF NON-RENAL CLEARANCE. THIS PHENOMENON CAN RESULT IN SEVERE CNS DEPRESSION. THE COMBINATION OF DEPAKENE AND PHENOBARBITAL HAS ALSO BEEN REPORTED TO PRODUCE CNS DEPRESSION WITHOUT SIGNIFICANT ELEVATIONS OF BARBITURATE OR VALPROATE SERUM LEVELS. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY. SERUM BARBITURATE LEVELS SHOULD BE OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE HAVE BEEN REPORTS OF BREAKTHROUGH SEIZURES OCCURRING WITH THE COMBINATION OF DEPAKENE AND PHENYTOIN. MOST REPORTS HAVE NOTED A DECREASE IN TOTAL PLASMA PHENYTOIN

CONCENTRATION. HOWEVER, INCREASES IN TOTAL PHENYTOIN SERUM CONCENTRATION HAVE BEEN REPORTED. AN INITIAL FALL IN TOTAL PHENYTOIN LEVELS WITH SUBSEQUENT INCREASE IN PHENYTOIN LEVELS HAS ALSO BEEN REPORTED. IN ADDITION, A DECREASE IN TOTAL SERUM PHENYTOIN WITH AN INCREASE IN THE FREE VS. PROTEIN BOUND PHENYTOIN LEVELS HAS BEEN REPORTED. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See "Adverse Reactions" section).

There have been reports of altered thyroid function tests associated with DEPAKENE. The clinical significance of these is unknown.

Carcinogenesis: DEPAKENE was administered to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 0, 80 and 170 mg/kg/day for two years. Although a variety of neoplasms were observed in both species, the chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving DEPAKENE and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving DEPAKENE. The actual incidence of fibrosarcomas in male rats was low with only two low dose and five high dose animals being affected. The presence of these tumors is not considered to be drug-related or of biological significance for the following reasons: (1) the overall low incidence, (2) the published variable incidence of spontaneously occurring fibrosarcomas and pulmonary adenomas in rats and mice respectively, (3) the long latency period of the neoplasms and (4) the fact that statistical significance of tumor incidence was present in males only. The significance of these findings for man is unknown at present.

Mutagenesis: Studies on DEPAKENE have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKENE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKENE (VALPROIC ACID) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

Pregnancy: See "Warnings" section.

Nursing Mothers: DEPAKENE is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Caution should be exercised when DEPAKENE is administered to a nursing woman.

ADVERSE REACTIONS

Since DEPAKENE (valproic acid) has usually been used with other antiepileptic drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to DEPAKENE alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other antiepileptic medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes," tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been noted in patients receiving valproic acid alone or in conjunction with phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation. (See "Drug Interactions" section). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia and bone marrow suppression have been reported.

Hepatic: Minor elevations of transaminases (e.g., SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally, laboratory test results include, as well, increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity. (See "Warnings" section).

Endocrine: There have been reports of irregular menses and secondary amenorrhea occurring in patients receiving DEPAKENE.

Abnormal thyroid function tests have been reported. (See "Precautions" section).

Pancreatic: There have been reports of acute pancreatitis occurring in patients receiving DEPAKENE.

Metabolic: Hyperammonemia. (See "Precautions" section).

Hyperglycinemia has been reported and has been associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

OVERDOSAGE

Overdosage with valproic acid may result in deep coma.

Since DEPAKENE is absorbed very rapidly, the value of gastric evacuation will vary with the time since ingestion. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of DEPAKENE overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of DEPAKENE it should be used with caution.

DOSAGE AND ADMINISTRATION

DEPAKENE (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day, until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) (15 mg/kg/day):

Weight (kg)	Weight (lb)	Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup Dose 1	Dose 2	Dose 3
10 - 24.9	22 - 54.9	250	0	0	1
25 - 39.9	55 - 87.9	500	1	0	1
40 - 59.9	88 - 131.9	750	1	1	1
60 - 74.9	132 - 164.9	1,000	1	1	2
75 - 99.9	165 - 197.9	1,250	2	1	2

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse reactions.

A good correlation has not been established between daily dose, serum level and therapeutic effect, however, therapeutic serum levels for most patients will range from 50 to 100 mcg/ml. Occasional patients may be controlled with serum levels lower or higher than this range.

As the DEPAKENE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See "Precautions" section).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

HOW SUPPLIED

DEPAKENE (valproic acid) is available as orange-colored soft gelatin capsules of 250 mg valproic acid in bottles of 100 capsules (NDC 0074-5681-13), in ABBO-PAC® unit dose packages of 100 capsules (NDC 0074-5681-11), and as a red syrup containing the equivalent of 250 mg valproic acid per 5 ml as the sodium salt in bottles of 16 ounces (NDC 0074-5682-16).

REFERENCES

1. Robert E, Guibaud P. Maternal Valproic Acid and Congenital Neural Tube Defects, *The Lancet*, 2(8304):937, 1982.
2. Centers for Disease Control. Valproic Acid and Spina Bifida: A Preliminary Report — France, *Morbidity and Mortality Weekly Report*, 31(42):565-566, 1982.

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